Remarks

Claims 116-121 have been added. Support for these amendments can be found throughout the specification and claims they depend on. No new matter has been added, and entry of these new claims is respectfully requested.

Claims 15-17, 23, 24, 26, 28, 34, 42-45, 48, 49, 51, 55, 62-64, 69, 92-100, 109 and 110 are withdrawn from consideration as being directed to a non-elected invention.

Claims 1-14, 18-22, 25, 27, 29-33, 35-41, 46-47, 50, 52-54 and 56-61 have previously been canceled without prejudice. Claims 73 and 104 are cancelled herein. Claims 72, 80, 82, 90, 103 and 105 are identified as withdrawn generic claims, with the provisionally elected invention now being covered by new claims 116-121.

Accordingly claims 65-68, 71, 74-79, 81, 83-89, 91, 101, 102, 105, 107, 108 and 111-121 are presented for consideration.

Election/Restriction

In their October 20, 2008 response, applicants provisionally elected, with traverse, Group I and, also with traverse, SEQ ID No. 25 (pending claims 65-68, 71, 74-79, 81, 83-89, 91, 101, 102, 105, 107, 108 and 111-121).

The Office emphasizes in the present Office Action that sequences 1-27 are considered different inventions. This is noted, as is the Office's acknowledgement in the restriction requirement of June 18, 2010, that, upon indication of the allowability of the generic claim(s), the restriction requirement between the sequences shall be withdrawn and any claim(s) depending from or otherwise requiring all limitations of the allowable linking claim(s) will be rejoined.

However, applicants would like to emphasize the following regarding Markush claims directed to **SEQ ID NOs: 24-27**.

The Office stated that PCT 13.2 and related guidelines require that all alternatives of a Markush group must share a common structure and property, and expressed the opinion that the claimed sequences SEQ ID NOs: 1-27 do not share a common structure. In response, applicants provisionally elected, with traverse, SEQ ID NO: 25. Markush claims 69, 72,73, 80, 82, 90, 103 and 105, which cover sequences in addition or other than SEQ ID NO:25, have been identified as withdrawn or have been cancelled. New claims 116-121 have been added, directed to SEQ ID NO: 25 only.

Although a provisional election of SEQ ID NO: 25 was made, applicants urge the Office to withdraw the restriction, if not with respect to SEQ ID NOs: 1-27, at the very least with respect to **SEQ ID NOs: 24-27**. Under PCT Rule 13.2, the requirement of a technical interrelationship shall be considered to be met when the alternatives of a Markush group are of a similar nature, i.e., share a common structure and activity related to that structure. Under this rule, in cases where the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art. Applicants would like to reemphasize that SEQ ID NOs: 24-27 are not only united by their source, i.e., they are all novel human MAR elements, they also share the common structure of being rich in AT and TA dinucleotides. Such structure is linked to their common "protein increasing activity greater than that of cLyMAR."

The Office expressed the opinion that the claimed sequences with different SEQ ID Nos do not share a common structure because they do not share a significant structural feature that is a contribution over the prior art. Applicants note that the Office's original restriction requirement (6/18/08) states that unity of invention exists when the same shared technical features of the alternatives results in a contribution over the prior art. In the 6/18/08 Restriction Requirement, the Office expressed the opinion that the technical feature of a bent DNA and a binding site for a DNA binding protein lacks inventive step or novelty in view of Kries et al., which was said to teach DNA comprising cLysMAR and a bent DNA sequence. Subsequently, applicants amended the claims so they share the common activity of increasing protein production to levels greater than those of cLysMAR.

The Office is now applying the reasoning of the 6/18/08 Restriction Requirement to the Markush groups, even though the claims were amended to include the activity of increasing protein production to levels greater than cLysMAR, a limitation clearly not disclosed by Kries et al. Previously, the special technical feature of the restricted groups was allegedly not distinctive over Kries et al.'s disclosure of the cLysMAR DNA. Now that the claims are amended to state specifically that the shared activity is greater than that of the prior art (cLysMAR) activity, these claims share structural features linked to a shared inventive and novel activity, i.e., the unexpected ability to increase the expression of transgenes to levels significantly above those disclosed in the cited art. Thus, applicants request that the restriction requirement be removed for claims directed to SEQ ID NOs: 24-27, which are claims 72, 80, 82, 90, 103, and 105, directed to SEQ ID NOs: 24-27, presently withdrawn.

New claims 116-121 have been added to cover SEQ ID NO: 25 specifically. These claims are supported by their original counterparts, i.e. claims 69 and 72 (new claim 116), 80 (new claim 117), 82 (New claim 118), 90 (new claim 119), 103 (new claim 120) and 105 (former 106) (new claim 121). Claims 69, 72, 80, 82, 90, 103 and 105 can thus be withdrawn. Applicants respectfully request reconsideration of the restriction requirement.

Specification

On page 3 of the Action, the Office objected to the disclosure because it contains an embedded hyperlink such as on page 3, line 2. Applicants have amended the specification to remove the embedded hyperlinks in paragraphs 84, 86, 213 and 228.

On page 4 of the Office Action, the Office noted that the trademark SMAR Scan® should be capitalized and accompanied by the generic terminology, as required by MPEP 608.01(v).

Applicants note that, pursuant to MPEP 608.01(v), the specification maintains the proprietary nature of the SMAR Scan® trademark by using the ® trademark registration symbol and by capitalizing "SMAR." Furthermore, SMAR Scan® is described generically in paragraph 84 and in those instances when used throughout the specification. Accordingly, Applicants respectfully submit that the proprietary nature of the SMAR Scan® trademark is preserved throughout the specification.

Claim Objections

On page 4, the Office objected to claims 69, 72, 73, 80, 82, 90, 103, 104,106 (now 105) and 107 for containing non-elected subject matter, i.e., to sequences other than SEQ ID NO: 25, and requires amendment of these claims so they are directed to elected inventions only. Applicants have partially cancelled these claims (73, 104). With the introduction of new claims 116-121 that only cover SEQ ID No. 25, claims 69, 72, 80, 82, 90, 103 and 105 can thus be withdrawn (claim 107 is not in issue anymore due to the amendment of claim 106). However, as indicated above, applicants urge the Office to reconsider in particular the restriction of the sequences set forth in claims 72, 80, 82, 90, 103 and 105 which also cover SEQ ID NOs: 24, 26 and 27, which applicants believe should be examined together with claim 25.

35 USC 112, FIRST PARAGRAPH REJECTION

On page 4, the Office rejected claims 65-91, 101-104 and 112-115 under 35 U.S.C., first paragraph, as failing to comply with the written description requirement.

The Office noted that the specification discloses sequences that have a high AT/TA value (mean around 35%), but expressed the opinion that the specification does not show that all sequences with 10% TA and/or 12% AT on a stretch of 100 base pairs and a DNA binding site would have protein producing increasing activity in any setting. The office cited the present application and Girod et al, 2007 (as cited in applicants IDS- hereinafter "Girod") as an example of the art at the time of filing (and later) not making up for deficiency of the specification for describing the structural element that is linked to the claimed function. The Office also used Girod to show that there allegedly is no consensus agreement that any of the specific DNA motifs may be ascribed to various activities of MARs, especially the protein expression enhancing activity.

Claim 65 requires the claimed purified and isolated DNA sequence to have:

a) at least one bent DNA element comprising at least 10% of the dinucleotide TA and/or at least 12% of the dinucleotide AT on a stretch of 100 contiguous base pairs; and

b) at least one binding site for a DNA binding protein,

wherein said purified and isolated DNA sequence has protein production increasing activity greater than that of chicken lysozyme MAR (cLysMAR). (*emphasis added*)

It is well established that possession of the claimed invention, the core of the written description inquiry, may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). (MPEP 2163) (*emphasis added*).

The Office focuses, among others, on the fact that Girod discloses a non-activator

sequence, 1-15, that has highly enriched AT and TA dinucleotides. However, Girod's method does not take advantage of the tool, including selection tool, provided and disclosed by the present specification to distinguish between functional and sequences that indeed "protein production increasing activity greater than that of chicken lysozyme MAR" (see definition in paragraph [0052] of the publication).

The specification provides, as the Office noted, a bioinformatic tool to retrieve relevant sequences. Example 6 details the identification of super MARs having AT dinucleotide frequences greater than 12% and TA dinucleotide frequences greater than 10% out of a total of 100 base pairs of DNA, with the most efficient MARs displaying mean values around 35% of the two nucleotide pairs.

In this example, 1757 potential super MARs are further selected using different criteria, in particular the MARs were checked for transcription factor binding sites and dinucleotide frequencies.

The specification provides tools to identify sequences that have "protein production increasing activity" (see definition of this term in paragraph [0052] of the publication of this application). Here the reader is specifically referred to Example 11 and Figure 13.

Finally, Example 16 shows that taken together the tools provided by the specification are able to identify some "super" MARs that increase the expression of a recombinant protein very significantly above the expression driven by the chicken lysosyme MAR.

With the disclosure provided by applicants, the species disclosed in the specification are of sufficient variety to reflect the variation within the genus to meet the standards set by the written description requirement.

Applicants note that the Office does not make any specific rejections of claims 112-115. In fact, the Office, on page 6 of the Office Action contrasts AT/TA values that are only slightly above (mean value around 35%) the "at least 33% TA/AT dinucleotides on a 100 base pair stretch" of these claims to the ones on which the rejection focuses, namely 10-12% AT/TA dinucleotides on a 100 base pair stretch. In view of the lack of any specific argument made against claims 112- 115, applicants have to assume that these claims indeed fall outside the rejection.

In view of the above arguments demonstrating applicants' possession of the invention in conformance with the written description requirement, applicants request reconsideration and withdrawal of the rejection of claims 65-91, 101-104 and 112-115 under 37 CFR 112, first

paragraph.

35 USC 112, SECOND PARAGRAPH REJECTION

On page 10, the Office rejected claims 65-91, 101-104 and 107 under 35 U.S.C., 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject mater which applicant regards as the invention.

The Office expressed the opinion that the term "cLysMAR" in claims 65 and 101, and thus dependent claims 66-91 and 101-104, renders these claims indefinite. Although abbreviation is permitted in the claims, the Office notes that the first appearance of the term should be spelled out.

In response, applicants have amended claim 65 to fully spell out the term chicken lysozyme MAR.

The Office rejected claim 107 because the term "BgIII-BamH1 linker". According to the Office, it is unclear whether the human MAR elements are "located between BgIII and BamHI or between BgIII and BamHI linkers on each side." According to applicants best understanding, claim 107 has been amended to clarify that the human MAR elements are located between BgIII- BamHI linkers.

The Office rejected claims 81 and 82 as having insufficient antecedent basis for the limitation, "said second purified and isolated DNA sequence" in line 1 because claim 74 only recites one purified and isolated DNA sequence. Applicants have amended claims 81 and 82 so that they depend on the appropriate claim, which is claim 75, thereby providing antecedent basis for the claim element to a second purified and isolated DNA sequence.

Applicants respectfully request that the Office withdraw the rejections to claims 65-91, 101-104 and 107 under 35 USC 112, second paragraph in view of the above amendments to the claims.

35 USC 102 REJECTION

On page 11, the Office rejected claims 105, 106 and 108 under 35 USC 102(b) as allegedly anticipated by **Klehr et al.** (see IDS), which is said to disclose synthetic MAR comprising human β-interferon domain MAR comprising linkers such as EcoRI and Bam HI. The specification is said to not describe what constitutes a variant of SEQ ID NO:25, leading the

Office to conclude that the MAR sequence disclosed in Klehr et al. meets this limitation of a variant.

Applicants amended claim 106 to be directed to SEQ ID NO: 25 and variants/fragments thereof, which Klehr et al. clearly does not disclose. Variants are described in the specification in paragraph [0044] of the publication of the present application as "nucleotide sequences that vary from the reference sequence by conservative nucleotice substitutions, whereby one or more nucleotides are substituted by another with [the] same charateristics." Fragments are described in paragraph [0051]. Applicants submit that Klehr et al. does not appear to disclose sequences that fall within this definition or the scope of the claim. In particular, the human β-interferon domain MAR of Klehr et al. would not be construed to be a variant of SEQ ID NO: 25, according to the definition in the specification. Thus, since each and every element as set forth in the claim is not found, either expressly or inherently, in Klehr et al., Klehr et al. does not anticipate claim 105.

Claim 108 has been further amended to specify that the MAR sequence has a protein production increasing activity greater than that of cLysMAR, a limitation not met by the sequences of Klehr et al (see definition of this term in paragraph [0052] of the publication of the present application).

In view of the above, applicants request the Office reconsider and withdraw the rejeciton of claims 105, 106 and 108 under 35 USC 102(b). Claim 107 can been withdrawn from consideration as containing not elected subject matter. However, reconsideration of the restriction requirement is respectfully requested (see above).

The Office also rejected claims 112-115 under 35 USC 102(b) as allegedly anticipated by **Michalowski et al.**, which the Office cited as disclosing isolated MAR DNA sequences comprising at least 33% of the dinucleotide and /or at least 33% of the AT on a stretch of 100 contiguous base pairs, and at least one binding site of a DNA binding protein, as well as vector constructs comprising a MAR and a gene of interest or multiple MARs. Furthermore, the Office expressed the opinion that Michalowski et al. disclose that MARs incease reporter expression in stably transformed cell lines.

Michalowski et al. disclose a percentage of AT only, not a percentage of AT dinucleotides or TA dinucleotides as set forth in the rejected claims. To anticipate, a disclosure

must teach each and every element set forth in the claim. Michalowski defines "AT rich regions" as sections of 20 contiguous nucleotides that are greater than or equal to 90% A and/or T nucleotides (col. 4, lines 44-45). Michalowski et al. does not refer to dinucleotides at all, but instead to A and/or T nucleotides and their overall content. Applicants submit that the Office has not shown and applicants could not find in an independent review that, Michalowski et al disclose sequences having at least 33% of the dinucleotide TA and/or at least 33% of the dinucleotide AT on a stretch of 100 contiguous bases, as required by claims 112-115.

In view of the above arguments, applicants request the examiner to withdraw the rejection of claims 112-115 under 35 USC 102(b).

35 USC 103 REJECTION

On page 12, the Office rejected claim 107 under 35 USC 103(a) as allegedly unpatentable over Klehr et al. because it allegedly would have been obvious to add a BglII – BamHI linkers to a synthetic MAR sequence based on the choice of appropriate multiple cloning sites on the vector.

Claim 107 depends from claim 106, which applicants have amended to be directed to SEQ ID NO: 25 and its variants and fragments. Klehr et al., as discussed above, does not teach SEQ ID NO: 25 or its variants, which the specification describes in paragraph 0044 as "nucleotide sequences that vary from the reference sequence by conservative nucleotice substitutions, whereby one or more nucleotides are substituted by another with [the] same charateristics." The human β-interferon domain MAR of Klehr et al. would not be construed to be SEQ ID NO: 25 or its variant, according to this definition in the specification. As Klehr et al. does not teach the MAR sequence SEQ ID NO:25, the basis of this obviousness rejection has been removed and the claim should be allowable.

Conclusion

For the reasons discussed above, applicants submit that all pending claims are in condition for allowance. Applicants respectfully request the withdrawal of all objections and rejections, and to allow this application to issue.

The Commissioner is authorized to charge fee deficiencies and overpayment in connection with this filing to undersign's deposit account 50-3135.

Respectfully submitted,
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